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Relationships Between Selected Gene Polymorphisms and Blood Pressure Sensitivity to Weight Loss in Elderly Persons With Hypertension

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Abstract

Salt sensitivity, the heterogeneity in the response of blood pressure (BP) to alterations in sodium intake, has been studied extensively, whereas weight sensitivity, the heterogeneity in BP response to weight change, has received scant attention. We examined the relationship of 21 gene polymorphisms previously found to be associated with hypertension, diabetes mellitus, or obesity, with weight sensitivity in the Trial of Nonpharmacologic Interventions in the Elderly, where participants with hypertension were randomized to receive intensive dietary intervention of sodium reduction, weight loss, both, or attention control, whereas pharmacological therapy was kept constant. After correcting for multiplicity, we identified significant associations of 3 polymorphisms with weight sensitivity of systolic BP (rs4646994, rs2820037, and rs1800629) and 3 polymorphisms for diastolic BP (rs4646994, rs2820037, and rs5744292). A recursive partitioning algorithm selected the combination of rs4646994, rs1800629, rs1982073, and rs1800896 as the set associated with the highest weight sensitivity. Polymorphisms related to hypertension, obesity, and diabetes mellitus are associated with weight sensitivity of BP.

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Disclosures

None.

Keywords

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Hypertension is a prevalent cardiovascular disease risk factor accounting for more death and disability than any other risk factor worldwide.[1–3] Evidence relating salt intake and body weight to blood pressure (BP) derives from animal studies, physiology, epidemiology, and clinical trials.[4–9] Salt sensitivity refers to heterogeneity among humans in their responses of BP to alterations in sodium and extracellular fluid volume status.[10–15] Gene polymorphisms and ethnic variation account for part of the variability in salt sensitivity.[16] Dietary sodium reduction and weight loss are effective in decreasing BP in patients with hypertension.[9,17,18] Although salt sensitivity has been studied extensively, weight sensitivity, the heterogeneity in BP response to weight change, has received scant attention.[19] Trial of Nonpharmacologic Interventions in the Elderly (TONE) tested whether sodium reduction or a weight loss program for obese participants would reduce the need for antihypertensive medication. In this study, compared with usual care, the need for antihypertensive therapy was lower after weight reduction or sodium reduction, with similar hazard ratios (0.60; 95% confidence interval, 0.45–0.80, and 0.64, 0.49–0.85, respectively).[20] The purpose of this study was to examine whether polymorphisms related to hypertension, obesity, and diabetes mellitus are associated with weight sensitivity or salt sensitivity of BP.

Methods

TONE tested the hypothesis that sodium reduction in participants with hypertension or a weight loss program for those who were obese would reduce the need for antihypertensive medication. Using a 2×2 factorial design, obese (body mass index [BMI]>27.8 kg/m^2 for men, 27.3 for women) participants were randomized to sodium reduction, weight loss, sodium reduction and weight loss combined, or attention control, whereas nonobese participants were randomized to sodium reduction or attention control for an average follow-up of 30 months. Men and women aged 60 to 80 years with systolic blood pressure (SBP) <145 mm Hg and diastolic blood pressure (DBP) <85 mm Hg on 1 or 2 antihypertensive medications were eligible to participate. Potential participants with serious cardiovascular disease, mental or physical illness, and insulin-dependent diabetes mellitus were excluded. The sodium-reduction goal was a 24-hour dietary sodium intake (by 24-hour urine sodium excretion) of 1800 mg (80 mmol) or less, and the weight loss goal was loss of 10 pounds or more. Participants randomized to attention control participated in meetings with lectures on topics not related to obesity, sodium intake, nutrition, or hypertension.

The intervention consisted of 3 phases (intensive, extended, and maintenance). The initial 4-month intensive phase provided participants with core knowledge and behavior skills, whereas the extended and maintenance phases focused on prevention of relapse. The data presented in this article pertain to the effect of the intensive intervention phase when participants received constant antihypertensive medication, while in the randomized dietary intervention. The first drug withdrawal visit for each patient occurred 76 to 104 days after the first group intervention session. Baseline values and the change in SBP, DBP, and BMI

between baseline and the first drug withdrawal visit were calculated for each participant. The change in 24-hour urine sodium between baseline and the 9-month follow-up visit was also calculated (24-hour urine sodium was not measured at the first drug withdrawal visit).

Selection of Candidate Polymorphisms

We searched the literature for gene polymorphisms pertaining to hypertension, obesity, and diabetes mellitus. The most frequently published polymorphisms, and polymorphisms from the Wellcome Trust Consortium, were used to select 21 polymorphisms for study. Polymorphism data were collected in 2 stages: data for 7 polymorphisms were collected for the analysis performed for a previous angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism,[19] and data for an additional group of 16 polymorphisms were collected in 2011, including 2 polymorphisms (rs699 and rs5370) from the initial group, for a total of 21. Information on polymorphisms was available for 722 participants. Four hundred eleven of the 722 (56.9%) participants had at least 1 missing value, among which 219 (30.3%) had only 1 missing value. The polymorphisms and their reported associations with hypertension, diabetes mellitus, and obesity are shown in Table 1. Missing values were assigned by Bayesian imputation, controlling for the polymorphisms with available data and race.[21]

Statistical Methodology

Linear Statistics—Modeling of SBP and DBP change was performed as a function of change in BMI or 24-hour sodium change and of the 21 polymorphisms chosen from the literature (Table 1), whereas controlling for participant characteristics and additional covariates.

Dependent Variables—The dependent variables were SBP_Change, the SBP at baseline minus the SBP at the first drug withdrawal visit; and DBP_Change, the DBP at baseline minus the DBP at the first drug withdrawal visit.

Independent Variables—The independent variables were subdivided into 5 groups:

(i). BMI-related covariates: Baseline_BMI and BMI_Change (from baseline to the first drug withdrawal visit).

(ii). Sodium-related covariates: Baseline 24-hour sodium and 24-hour_urine_sodium_Change (from baseline to the 9-month follow-up visit).

(iii). Genotype: 21 polymorphisms: The most important group of independent variables were the 21 polymorphisms denoted by $I_1,..., I_{21}$, where each I^i is a categorical variable taking values 1, 2, or 3 corresponding to wild type, heterozygous, and homozygous mutant, respectively. These independent variables were entered into the model either one at a time or all together.

(iv). Basic covariates: age and sex were included in all models.

(v). Investigator-selected covariates were 28 clinical covariates hypothesized to be related to SBP_Change, DBP_Change, and weight sensitivity. We ran a variable selection procedure, including variables listed under (i) to (v) using glmnet (a

procedure designed to perform variable selection when the independent variables are correlated among themselves; Table S1 in the online-only Data Supplement).[22]

Data Subsets—The datasets analyzed were based on 6 randomized groups (a–f): (a) Obese participants, combined (sodium reduction and weight loss) intervention (n=112); (b) Obese participants, weight loss (n=112); (c) Obese participants, sodium reduction (n=99); (d) Obese participants, attention control (n=109); (e) Normal weight participants, sodium reduction (n=156); and (f) Normal weight participants, attention control (n=134). Seven subsets were defined as follows: (1) attention control (d and f); (2) weight loss (b); (3) sodium reduction (c and e); (4) combined intervention (a); (5) all sodium reduction (a, c, and e); (6) all weight loss (a and b); and (7) all participants (a–f).

Models—Six types of models were generated using combinations of the above groups:

Model 1: One polymorphism at a time+Baseline_BP+BMI_ Change+Baseline_BMI +24-hour_urine_sodium_Change+Baseline_24-hour_urine_sodium (examines weight and salt sensitivity)

Model 2: All polymorphisms+Baseline_BP+BMI_Change+ Baseline_BMI+24-hour_urine_sodium_Change+Baseline_ 24-hour_urine_sodium (examines weight and salt sensitivity)

Model 3: One polymorphism at a time+Baseline_BP+BMI_ Change+Baseline_BMI (examines weight sensitivity)

Model 4: All polymorphisms+Baseline_BP+BMI_Change+ Baseline_BMI (examines weight sensitivity)

Model 5: One polymorphism at a time+Baseline_BP+24-hour_ urine_sodium_Change +Baseline_24-hour_urine_sodium (examines salt sensitivity)

Model 6: All polymorphisms+Baseline_BP+24-hour_urine_sodium_Change +Baseline_24-hour_urine_sodium (examines salt sensitivity)

The 6 models were run with and without the investigator-selected covariates shown in independent variable list (v) above, yielding 12 linear models. Each model was run twice, once for SBP and once for DBP, for each of the 7 datasets (a total of 168 runs).

Recursive Partitioning Model—Although trees with splits based on polymorphisms have been used to predict the risk of coronary artery disease,[23] the methodology used here is different. We built trees using only the polymorphisms to split the nodes with the other independent variables as the splitting criteria based on linear models 2, 4, and 6 described above.

Each tree yielded a partition of the data into *m* subsets that included individuals with a certain genotype, such that the relationship between SBP_Change (or DBP_Change) and BMI_Change (or 24-hour_urine_sodium_Change) follows a similar slope. Subsets of high interest are those with slopes significantly higher or lower than the average.

Polymorphisms were coded as: 1=Wild Type, 2=Heterozygous, or 3=Homozygous mutant. The partitions split the data into 2 groups in all 3 possible ways (1 versus 2 and 3, 2 versus 1 and 3, or 3 versus 1 and 2), and the partition that resulted in the biggest improvement in the R^2 was chosen in each case.

Results

Of the 722 patients included in this study, 51.7% were men and the average age was 66±4.7 (median, 65; range, 60–80; interquartile range, 62–69). Five hundred thirty-eight (74.5%) were white and 181 (25.1%) were black. Two hundred forty-three were in the attention control group, 112 in the weight loss group, 255 in the sodium reduction group, and 112 in the combined intervention group. Baseline and first drug withdrawal visit BP, BMI, and urine sodium data are presented in Table S2. SBP_Change was –3.30±1.28 mm Hg in the weight loss group and –2.58±0.79 mm Hg in the sodium-reduction group. BMI_Change was –1.55±0.10 kg/m^2 in the weight loss group and 24-hour_urine_sodium_Change was 49.15±4.00 mmol/24 hours in the sodium-reduction group (Table S2).

Linear Statistics

Selection of Clinical Variables—The glmnet procedure selected diabetes mellitus, current smoking, history of stroke >6 months before randomization, number of blocks walked per day, rate of physical activity during the year before being randomized, hours of moderate physical activity per week, hours of light physical activity per week, having a child with diabetes mellitus, and having a father with renal failure (Table S1).

Categorical Predictions Using Linear Models—Table 2 shows an array of linear model results, with 12 columns representing the 12 types of linear models for SBP. The rows are grouped in 7 blocks corresponding to the 7 datasets described in the methods. Each block shows the reference numbers of the polymorphisms and probability values of the associations that were statistically significant at the 0.1 level for the corresponding combination of column model type and row dataset. The data on the left of Table 2 are results of models adjusted for both 24-hour urine sodium and BMI, for 24-hour urine sodium only, and for BMI only, in each case without other covariates. Results of models considering both one polymorphism at a time, and all 21 polymorphisms are shown for each model type. Associations with probability values <0.1 are shown. The data on the right are results of models adjusting for sodium and BMI, sodium only, and BMI only, with the addition of the investigator-selected covariates. The results for weight sensitivity and salt sensitivity of DBP are shown in Table S3.

Controlling for Multiplicity—Predicted false discoveries and observed discoveries of associations of polymorphisms with SBP_Change or DBP_ Change in relation to BMI_Change and sodium reduction are shown in Tables S4 and S5. An issue with the analyses is the potential for spurious associations given the large number of comparisons performed. One approach to avoid this issue is to use Bonferroni correction to the α level and produce far more stringent criteria for significance. This would be appropriate, if the probability values were mutually independent. In this analysis, the polymorphisms are

correlated, making the Bonferroni correction too strict. Instead, we calculated the number of false discoveries using our own adaptation of the Hochberg and Benjamini[24] false discovery rate and applied it to our set of associations of polymorphisms. We simulated a set of hypothetical participants, where the genotype of each actual participant was linked to a randomly selected phenotype (all other variables). This process generated a null hypothesis in the sense that the genotype of each simulated participant had no relation to the phenotype, including the response variables SBP_Change and DBP_ Change. Therefore, any significant associations of polymorphisms with the other variables in this new random dataset would be false discoveries. We repeated this randomized simulation 100 times to estimate the number of expected false discoveries. We estimated the number of truly signifi-cant observed associations as the number of observed significant associations minus the number of false discoveries (at the median) at a given probability value. Tables S4 and S5 show the 50th and 80th percentiles of counts of false discoveries generated from 100 simulations of the random dataset for SBP (Table S4) and 100 simulations for DBP (Table S5). For both SBP and DBP, the third column shows the number of actual discoveries to compare with the false discoveries to estimate how many true discoveries (associations) are present in each case. Tables S4 and S5 were used in combination with Table 2 and Table S3 to determine which associations of polymorphisms with BP changes should be considered true discoveries and which are suspect of being false discoveries.

Summary of Data Obtained From Linear Statistical Analyses

In Table S6, we summarize the significant associations between the polymorphisms with SBP_Change and DBP_Change that were found by the linear models. The rule that we followed to select significant associations of polymorphisms with weight sensitivity and salt sensitivity was a combination of ranking the polymorphisms by the probability values of their associations with SBP_Change or DBP_Change, and correcting the list by eliminating the least significant polymorphisms according to the number of false discoveries.

In linear statistical analyses of the randomized groups of TONE, examining each polymorphism separately, we observed an association of weight sensitivity (BP change for a given change in BMI) with 5 polymorphisms with respect to SBP (rs1800629, rs4646994, rs5186, rs2820037, and rs1800872). Associations with DBP were observed for 6 polymorphisms (rs4646994, rs2820037, rs4684847, rs11110912, rs5744292, and rs4961). Among participants randomized to the combined intervention (both weight loss and sodium reduction), rs1800629 and rs2820037 were associated with weight sensitivity of SBP, and rs5744292 with weight sensitivity of DBP.

With respect to weight sensitivity and considering the simulation results of the random dataset (false discoveries) shown in Tables S4 and S5 and the results of the linear models (Table 2 and Table S3), 4 significant associations of polymorphisms with BP change (SBP or DBP) were identified. The rs4646994, an insertion deletion polymorphism of the angiotensin-converting enzyme and rs2820037, related to the ryanodine receptor 2, were significantly associated with weight sensitivity for both SBP and DBP. The rs1800629, related to tissue necrosis factor-α, was associated only with SBP and rs5744292, related to interleukin-18, only with DBP (Table 3). This table shows associations of polymorphisms

and pathways of weight sensitivity and salt sensitivity observed in TONE, and corresponding data reported by previous investigators on salt sensitivity. Figure S1 shows box plots of weight sensitivity and salt sensitivity for selected polymorphisms.

In the groups randomized to sodium reduction, salt sensitivity was associated with 4 polymorphisms with respect to SBP (rs6997709, rs4646994, rs5443, rs4684847), and with 3 polymorphisms with respect to DBP (rs5370, rs7961152, rs5744292). Polymorphisms rs6997709, related to potassium channel KCNK9, and rs4684847, related to PPAR-γ, had the strongest associations with salt sensitivity of SBP, and rs7961152, related to branched chain amino acid transaminase 1, and rs5744292, related to interleukin-18, with salt sensitivity of DBP (Table 3). Polymorphism rs5744292 was associated with both weight sensitivity and salt sensitivity of DBP.

Recursive Partitioning Model

The results of the recursive partitioning model for SBP and for DBP are shown in the online-only Data Supplemental Table S7. The algorithm produced 18 trees for SBP and 20 for DBP. Three of the 4 polymorphisms associated with weight sensitivity of SBP in the linear models (rs4646994, rs1982073, and rs1800896) were also selected by the recursive partitioning model as the combination with the highest SBP_Change per BMI_Change in the weight loss group. The slope increased with successive additions of polymorphisms from 3.51 mm Hg/kg per m^2 in the initial division (rs4646994, 75 patients) to 5.55 mm Hg/kg per m^2 (rs1800629, 49 patients), to 6.02 mm Hg/kg per m^2 (rs1982073, 41 participants), to 6.51 mm Hg/kg per m^2 (rs1800896, 31 patients; the online-only Data Supplemental Figure S2). The rs1800896 was also selected for weight sensitivity of DBP.

Discussion

This study shows significant associations of polymorphisms with the BP response to weight loss. After correction for multiplicity and adjustment for the expected false discoveries resulting from the large number of analyses, we identified 7 polymorphisms with significant associations for weight sensitivity. Two (rs2820037 and rs4646994) were associated with weight sensitivity of both SBP and DBP. In addition, one (rs1800629) was associated only with weight sensitivity of SBP, and another one (rs5744292) only with that of DBP.

Similar sets of polymorphisms were associated with weight sensitivity of SBP and DBP. Different associations or strengths of the associations for SBP and DBP with salt sensitivity were observed in the GenSalt study.[25] It is possible that the polymorphisms that were identified as associated with weight or salt sensitivity could have been merely linked to causal variants, rather than causing variability in weight (and salt) sensitivity themselves.[26]

Although associations with the exact polymorphisms reported for salt sensitivity in TONE were not observed in the GenSalt cohort, polymorphisms affecting the same genes or pathways were observed for all 4 polymorphisms associated with weight and salt sensitivity as shown in Table 3.[27–33] It is possible that the polymorphisms or causal variants linked to them affect BP and weight and salt sensitivity through a complex interplay of vasoconstrictive and vasodilating substances interacting with the autonomic nervous system.

The recursive partitioning model identified that participants who had 2 of the 3 polymorphisms selected by the linear statistics had the highest weight sensitivity with a slope of 6.51.

Rhee and associates performed a controlled study of salt sensitivity in Korea, examining 36 polymorphisms previously reported to be associated with hypertension on 101 participants using ambulatory BP measurement.[33] They examined 2 (rs6997709 and rs5744292) of the 4 polymorphisms significantly associated with salt sensitivity in TONE and found a significant association of one of them (rs5744292; odds ratio, 4.9; 95% confidence interval, 1.5–15.5; *P*=0.007).

The 2002 paper reported that I/D polymorphism of ACE was related to weight sensitivity.[19] The present report expands on this finding by examining and adjusting for 20 additional polymorphisms and evaluating combinations of polymorphisms. One polymorphism examined in our study (rs5744292, related to interleukin-18) was associated with both weight sensitivity and salt sensitivity. Chen and associates have reported increased sodium sensitivity among individuals with the metabolic syndrome.[15] We observed a significant association of the ACE I/D polymorphism (rs4646994) with weight sensitivity, but not with salt sensitivity. Zhang et al found that the ACE ID+II genotype interacted with daily salt intake and correlated with hypertension (*P* for interaction=0.047), and that BP was increased by high salt intake (*P*=0.005), whereas in the DD genotype it was not (*P*=0.257).[31] This interaction was more prominent in the overweight group (*P*=0.039).

Limitations of the study include the fact that it is retrospective, and that the number of participants is small relative to the number of polymorphisms. Although the period under study was between randomization and the first drug withdrawal visit, information on 24-hour urine sodium was not available at the latter visit, as it was not collected during TONE. We substituted 24-hour urine sodium at the 9-month visit based on our finding that the change in 24-hour urine sodium between 9 and 18 months was small (45.2 versus 44.6 mmol/day, 1.3%),[20] and that the average time interval between the first drug withdrawal visit and the 9-month visit was approximately 5 months (161±18.9 days; median, 161; interquartile range, 149–175).

Additional limitations are related to different temporal patterns of weight change and changes in physical activity among TONE participants.[34] The missing data on individual polymorphism values is another limitation that we addressed with Bayesian imputation.

Strengths of the study include the precision of the clinical data collected during a randomized controlled observer-blind clinical trial, and that clinically relevant changes in body weight and salt intake were achieved. Also, these data from TONE are the only data describing weight sensitivity in hyper-tension. Additional strengths of this article are the statistical techniques used to overcome multiplicity and the recursive algorithm to examine combinations of individual polymorphisms, rather than only 1 polymorphism at a time.

In the last 50 years, great progress has been made in the identification of risk factors for cardiovascular disease, and in proving that control of these risk factors accrues significant clinical benefits from the points of view of morbid events as well as mortality. In addition,

genomic studies have become more practical, faster, and less expensive.[26] Thus, evaluation of weight sensitivity may be a way to identify individuals who may benefit more from weight loss as compared with other lifestyle interventions (eg, sodium reduction).

Perspectives

In conclusion, polymorphisms related to hypertension, obesity, and diabetes mellitus are associated with weight sensitivity of BP. Similar sets of polymorphisms are associated with weight sensitivity of SBP and DBP. This study addresses an issue that has received scant attention in the past. These results may help to clarify the pathophysiology of hypertension in some patient subsets and to identify individuals who are more likely to benefit from weight loss. Examination of additional polymorphisms or genome-wide association studies and study of the relationship of weight sensitivity to demographic, medication, and other patient characteristics may also be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

- Although salt sensitivity has received considerable attention for >20 years, there is little information on the heterogeneity in the response of blood pressure to weight loss (weight sensitivity).
- Polymorphisms related to hypertension, obesity, and diabetes mellitus are associated with weight sensitivity of blood pressure.

What Is Relevant?

- These findings may be useful in clarifying the pathophysiology of hypertension in some patient subsets.
- Evaluation of weight sensitivity may help identify individuals who may benefit more from weight loss as compared with other lifestyle interventions.

Summary

We identified significant associations of polymorphisms related to hypertension, obesity, and diabetes mellitus with weight sensitivity of blood pressure.

Table 1

List of Selected Polymorphisms and Published Associations With Obesity, Diabetes Mellitus, and Hypertension

Genes	Polymorphism	Gene/Pathway	Obesity	Diabetes Mellitus	Hypertension
rs5370	G/T	Endothelin-1		X	X
rs1800796	C/G	Interleukin-6	X	X	X
rs7961152	A/C	BCAT1*			X
rs6997709	G/T	KCNK9†			X
rs4646994	I/D	ACE	X	X	X
rs5186	A/C	AT2R1‡			X
rs2820037	A/T	RYR2§	X		X
rs5443	C/T	GNB3//	X	X	X
rs1937506	G/T	Endothelin-1¶			X
rs1800629	G/A	TNF-α#	X	X	
rs4684847	C/T	PPAR-γ	X	X	X
rs11110912	C/G	MYBPC1**			X
rs1799983	G/T	NOS3	X	X	X
rs1800872	A/C	Interleukin-10		X	
rs5744292	G/C	Interleukin-18	X	X	X
rs699	A/C	Angiotensinogen (AGT)	X		X
rs4961	G/T	α-Adducin	X		X
rs1800795	C/G	Interleukin 6		X	X
rs1982073	C/T	TGF-β1	X	X	X
rs1800896	A/G	Interleukin-10		X	X
rs187238	C/G	Interleukin-18		X	X

*Branched-chain amino acid transaminase 1.

†Potassium channel subfamily K member 9.

‡Angiotensin II type 1 receptor (AGTR1) gene.

§Ryanodine receptor 2.

//Guanine nucleotide binding protein beta polypeptide 3.

¶Endothelin-1/C198.

#(G-308A) TNF promoter.

**Myosin-binding protein C, slow-type.

Table 2

Associations of Gene Polymorphisms With the Relationship of SBP Change vs BMI and 24-Hour Sodium Change*

		Na+Wt		Wt Only		Na Only			Na+Wt+ Investigator-Selected		Wt Only+ Investigator-Selected		Na Only+ Investigator-Selected	
Group	**Polymorphism**	**One**	**All**	**One**	**All**	**One**	**All**	**Polymorphism**	**One**	**All**	**One**	**All**	**One**	**All**
Group 1: Control	rs5370	0.004	0.005	0.018	0.023	0.002	0.003	rs5370	0.059	0.065			0.039	0.046
	rs1800796	0.018	0.020			0.017	0.018	rs7961152				0.034		
	rs1800795	0.093						rs1799983	0.025	0.076	0.044		0.020	0.056
	rs1800896		0.085				0.096							
	rs7961152		0.086	0.086	0.018									
	rs11110912		0.090		0.073		0.097							
	rs1799983	0.058		0.083		0.051								
Group 2: Wt Only	rs4646994	0.010	0.010	0.020	0.017	0.012	0.009	rs4646994	0.013	0.020	0.025	0.028	0.015	0.018
	rs4961	0.092		0.098		0.096		rs5186	0.077		0.038		0.081	
	rs5186	0.057		0.027		0.059		rs2820037	0.039	0.036	0.040	0.014	0.042	0.033
	rs2820037	0.029	0.010	0.030	0.005	0.032	0.010	rs6997709	0.091				0.095	
	rs6997709	0.088	0.098			0.093	0.096	rs1800872				0.091		
	rs1800872		0.096		0.077		0.095							
Group 3: Na Only	rs4646994	0.086	0.096	0.048	0.053	0.089	0.097	rs4646994	0.050	0.063	0.025	0.032	0.052	0.065
	rs5443	0.053	0.086	0.027	0.043	0.055	0.088	rs5443	0.058	0.098	0.029	0.048	0.060	0.100
	rs1800896				0.072			rs7961152		0.091		0.095		0.094
	rs4684847	0.024	0.083	0.047		0.025	0.084	rs4684847	0.021		0.039		0.022	
	rs6997709	0.001	0.004	0.006	0.028	0.001	0.004	rs6997709	<0.001	0.004	0.003	0.030	<0.001	0.004
Group 4: Both Na+Wt	rs2820037	0.016	0.032	0.018	0.038	0.014	0.032	rs2820037	0.027	0.047	0.024	0.038	0.028	0.061
	rs11110912			0.061		0.092		rs5744292	0.091					
	rs1800629	0.013	0.003	0.015	0.009	0.014	0.005	rs11110912	0.061		0.028		0.062	
								rs1800872	0.066		0.077		0.078	
Group 5: All Na	rs4646994	0.016	0.016	0.018	0.018	0.023	0.023	rs4646994	0.006	0.007	0.006	0.008	0.009	0.011
	rs5443	0.035	0.042	0.040	0.056	0.036	0.041	rs699			0.063			
	rs2820037						0.096	rs1982073			0.089	0.090		
	rs4684847	0.004	0.003	0.007	0.005	0.004	0.003	rs2820037						0.096
	rs1937506	0.022	0.056	0.047		0.028	0.066	rs7961152	0.085		0.043	0.048	0.098	

		Na+Wt		Wt Only		Na Only			Na+Wt+ Investigator-Selected		Wt Only+ Investigator-Selected		Na Only+ Investigator-Selected	
Group	**Polymorphism**	**One**	**All**	**One**	**All**	**One**	**All**	**Polymorphism**	**One**	**All**	**One**	**All**	**One**	**All**
	rs6997709	0.003	0.057	0.009	0.082	0.003	0.048	rs4684847	0.007	0.010	0.013	0.015	0.008	0.011
	rs11110912			0.083				rs11110912			0.068			
								rs6997709	0.006	0.039	0.017	0.08	0.006	0.034
Group 6: All Wt	rs2820037	0.002	0.001	0.001	0.001	0.002	0.001	rs2820037	0.002	0.001	0.001	<0.001	0.002	0.001
	rs1937506	0.070		0.039		0.089		rs5744292	0.050				0.061	
	rs11110912		0.089	0.069	0.050		0.076	rs11110912	0.084	0.055	0.030	0.031	0.080	0.047
	rs1800629	0.018	0.014	0.029	0.031	0.022	0.022	rs1800629	0.060	0.054	0.074	0.067	0.074	0.071
	rs1800872		0.068		0.046		0.082	rs1800872	0.030	0.030	0.025	0.011	0.034	0.040
Group 7: All	rs4646994	0.026	0.026	0.017	0.016	0.039	0.039	rs4646994	0.053	0.052	0.050	0.047	0.079	0.077
	rs5370	0.028	0.036	0.042	0.052	0.021	0.024	rs699	0.093		0.048	0.056		
	rs2820037	0.072	0.047	0.057	0.048	0.074	0.051	rs5370	0.085	0.077		0.093	0.067	0.055
	rs1800896				0.089			rs2820037		0.057	0.087	0.059		0.066
	rs7961152			0.027	0.030			rs1800896		0.092		0.067		0.095
	rs4684847	0.020	0.031	0.018	0.021	0.023	0.037	rs7961152	0.030	0.024	0.007	0.005	0.051	0.042
	rs1937506	0.067	0.040	0.088	0.065	0.064	0.037	rs4684847	0.026	0.053	0.021	0.036	0.030	0.063
	rs11110912			0.047	0.085			rs11110912			0.058	0.098		
								rs6997709	0.059	0.045	0.054	0.024	0.068	0.051
								rs1800872	0.093	0.090		0.045	0.061	0.073

BMI indicates body mass index; and SBP, systolic blood pressure.

The table includes polymorphisms that were associated (P<0.1) with weight and salt sensitivity using linear statistics, as described in detail on page 6.

*Changes between baseline and first drug withdrawal visit for SBP and BMI between baseline and 9-month visit for 24-hour sodium.

Table 3

Statistically Significant Categorical Predictions in TONE by Individual Polymorphisms/Genes/Pathways and Related Previously Reported Associations

Polymorphism	Gene/Pathway	SBP Weight Sensitivity	DBP Weight Sensitivity	SBP Salt Sensitivity	DBP Salt Sensitivity	Gene/Pathway	Reference #
rs4684847	PPAR-γ			0.004		PPAR-γ	27
rs6997709	KCNK9			0.003		TGF-β and K+	28
rs1800629	TNF-α	0.018				TNF-α and insulin resistance	29
rs2820037	RYR2	0.002	0.005			RYR2 and hypertension	30
rs4646994	ACE	0.01	0.004			ACE	31
rs5744292	IL-18		0.0001		0.005	IL-18 and hypertension and sudden death	32
rs7961152	BCAT1				0.03	BCAT1 and salt sensitivity	33

DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

P values correspond to a single polymorphism model adjusting for the basic covariates.